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Surviving sepsis campaign: research priorities for sepsis and septic shock

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Abstract

Objective: To identify research priorities in the management, epidemiology, outcome and underlying causes of sepsis and septic shock.

Design: A consensus committee of 16 international experts representing the European Society of Intensive Care Medicine and Society of Critical Care Medicine was convened at the annual meetings of both societies. Subgroups had teleconference and electronic-based discussion. The entire committee iteratively developed the entire document and recommendations.

Methods: Each committee member independently gave their top five priorities for sepsis research. A total of 88 suggestions (ESM 1 - supplemental table 1) were grouped into categories by the committee co-chairs, leading to the formation of seven subgroups: infection, fluids and vasoactive agents, adjunctive therapy, administration/epidemiology, scoring/identification, post-intensive care unit, and basic/translational science. Each subgroup had teleconferences to go over each priority followed by formal voting within each subgroup. The entire committee also voted on top priorities across all subgroups except for basic/translational science.

Results: The Surviving Sepsis Research Committee provides 26 priorities for sepsis and septic shock. Of these, the top six clinical priorities were identified and include the following questions: (1) can targeted/personalized/precision medicine approaches determine which therapies will work for which patients at which times?; (2) what are ideal endpoints for volume resuscitation and how should volume resuscitation be titrated?; (3) should rapid diagnostic tests be implemented in clinical practice?; (4) should empiric antibiotic combination therapy be used in sepsis or septic shock?; (5) what are the predictors of sepsis long-term morbidity and mortality?; and (6) what information identifies organ dysfunction?

Conclusions: While the Surviving Sepsis Campaign guidelines give multiple recommendations on the treatment of sepsis, significant knowledge gaps remain, both in bedside issues directly applicable to clinicians, as well as understanding the fundamental mechanisms underlying the development and progression of sepsis. The priorities identified represent a roadmap for research in sepsis and septic shock.

Keywords: Sepsis, Septic shock, Research, Priorities, Surviving Sepsis Campaign

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Introduction

Sepsis is life threatening organ dysfunction caused by a dysregulated host response to infection [1]. Sepsis is a global public health emergency, affecting millions of

people worldwide, and representing one of the largest causes of death across the world [2].

The Surviving Sepsis Campaign is dedicated to reducing mortality from sepsis. The campaign has released four sets of guidelines over the last 14 years, with the most recent being published in 2016 [3]. The 2016 Surviving Sepsis Guidelines consist of 93 statements on the early management and resuscitation of sepsis and septic shock, of which 32 are strong recommendations (7 based upon high evidence, 21 based upon moderate evidence and 4 based upon low evidence), 39 are weak recommendations (7 based upon moderate evidence, 32 based upon low or very low evidence) and 18 are best practice statements. Following recommendations contained within the Surviving Sepsis guidelines has been associated with improved outcomes [4, 5]. However, gaps in the data frequently exist, leading to insufficient clarity on many elements of sepsis management and precluding recommendations on many topics. Notably, the Surviving Sepsis Campaign guidelines are designed to assist bedside practitioners in the treatment of patients with sepsis and septic shock and therefore are restricted solely to management issues.

In an attempt to determine priorities for research within the field of sepsis, the Surviving Sepsis Campaign created a research committee that was explicitly charged with developing a list of research priorities related to sepsis. The intention was to address all aspects of sepsis. Thus while bedside management of sepsis played a key role, the committee also covered topics that are not part of the guidelines, including fundamental mechanisms underlying the development and progression of sepsis and septic shock. Understanding that possibilities for research within the broad field of sepsis are nearly limitless, the goal of this document is for the Surviving Sepsis Campaign to identify research priorities for improving understanding of and outcomes from sepsis.

Methods

Sponsorship

Funding for the research priorities was provided solely by SCCM and ESICM. No outside funding was received.

Selection and organization of the committee

The presidents of ESICM and SCCM appointed seven members (including one co-chair DDB and CMC, respectively) from each society in 2016 to the committee. In addition, the co-chairs of the Surviving Sepsis Campaign guidelines (LE, AR) were added as ad hoc members to the committee. Committee members were chosen based upon expertise in a wide variety of topics related to sepsis. As such, while many of the members of the research committee were authors on the Surviving Sepsis Campaign guidelines, many were not authors, so as to include expertise in areas not covered within the guidelines. In keeping with a commitment to diversity from both SCCM and ESICM, diversity (broadly defined but including geographic, gender, profession, specialty, socioeconomic) was expressly considered when populating the committee.

Determination of research questions and priorities

Each task force member was asked to submit five research questions on any subject related to sepsis. Respondents were instructed to pick the topics they felt were most important, explicitly not restricting this to any particular area. As such, the questions were not limited to areas of patient management (as covered by the Surviving Sepsis Campaign guidelines [3]) or definitions (as covered in the recent Sepsis 3 definitions [1]). The expectation was this open-ended approach would yield questions spanning the entire potential gamut of research related to sepsis. A total of 88 questions were narrowed to 26 questions (Fig. 1) based upon a voting prioritization process detailed in supplemental methods ESM 2.

The entire committee was subsequently asked to rank their top three research priorities in order from all subgroups except basic/translational science. The reason for excluding the basic/translational subgroup from the ranking of research priorities is the committee did not feel it was possible to directly compare the other six subgroups (which relate to critically ill patients at the bedside currently) to the more mechanistic and fundamental questions asked in basic/translational science (which relate to understanding sepsis better but cannot be used at the bedside currently). Choices were weighted so that each respondent's first choice was worth three points, second choice was worth two points and third choice was

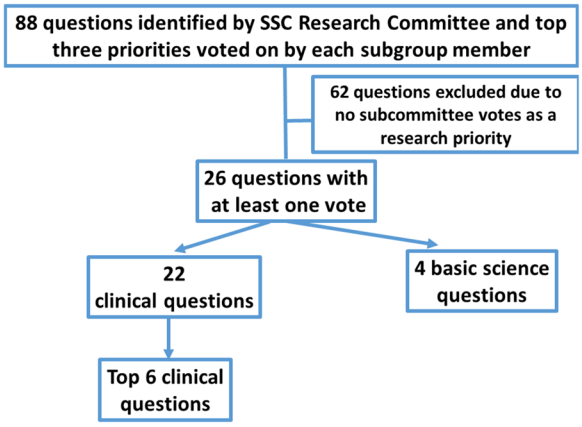

Fig. 1 Flowchart identifying process of narrowing to top research questions

Table 1 Top research priorities

Can targeted/personalized/precision medicine approaches determine which therapies will work for which patients at which times?
What are ideal endpoints for volume resuscitation and how should volume resuscitation be titrated?
Should rapid diagnostic tests be implemented in clinical practice?
Should empiric antibiotic combination therapy be used in sepsis or septic shock?
What are the predictors of sepsis long-term morbidity and mortality?
What information identifies organ dysfunction?

Table 2 Basic science questions

What mechanisms underlie sepsis-induced cellular and sub-cellular dysfunction?
How does sepsis alter bio-energetics and/or metabolism (both enhancement and failure)?
How does sepsis (and/or approaches used to manage sepsis) alter phenotypes and interactions in the host microbiome and do alterations in the microbiome effect outcomes
What mechanisms initiate, sustain and terminate recovery?

worth one point. The initial goal was to generate a top five priority list; however, a three-way tie for the fourth place resulted in the final top six priority list (Fig. 1). Of note, nine different questions received a first choice vote. A total of 13/16 first choice votes are represented in the top six priorities, and no question outside of the top six priorities received more than two votes total (and no question outside of the top six received more than a single first choice vote).

Conflict of interest policy

No industry input into the research priorities was obtained, and no industry representatives were present at any point in the process. No members of the research committee received financial compensation or honoraria of any type for their participation on the committee.

The process relied on personal disclosure in an identical manner to the Surviving Sepsis Campaign guidelines. No attempt was made by the group to seek additional information on self-reported conflict of interest.

Results

Top six research priorities

While each of the 26 research questions below were felt to be important (ESM 3), the committee felt it was appropriate to include a list of the top priorities distinct from basic/translational science. A list of the top six research priorities was therefore generated based upon a vote of the entire committee (Table 1). These priorities are not presented in order of importance, as we did not attempt to discriminate the relative importance of the top six research priorities. Although there was no intent to highlight any specific subgroups in the top priorities, they were nearly evenly distributed from the subgroups including infection (two priorities), fluids and vasoactive agents, adjunctive therapy, scoring/identification, and post-intensive care unit. The only subgroup that was not represented was administration/epidemiology. Since basic/translational science was felt to be distinct enough as to not be comparable, the four questions in this group (Table 2) were not ranked but are felt to be of equal importance in a complementary fashion.

Infections

Should empiric antibiotic combination therapy be used in sepsis or septic shock?

What is known Early institution of adequate antimicrobial therapy is associated with decreased mortality in septic patients [6, 7]. Combination therapy is defined herein as the use of two different classes (usually of different mechanistic classes) of antimicrobial agents for a single pathogen. There are two possible reasons for using combination therapy—(a) to accelerate pathogen clearance rather than to broaden antimicrobial coverage or (b) to assure that one pathogen is sensitive to the antibiotic, in light of significant microbial resistance. The most common therapy combinations include a beta-lactam with an aminoglycoside, fluoroquinolone or macrolide. It is important to note that sensitivity of microbes to these antibiotics varies locally, and this should be taken into account prior to prescribing combination therapy. Combination therapy must be distinguished from broad spectrum antibiotics (i.e. a single gram positive agent, a single gram negative agent, a single anti-fungal agent).

A propensity-matched analysis and a meta-analysis/meta-regression analysis have been performed examining the efficacy of combination therapy when used to accelerate pathogen clearance [8, 9]. These show improved survival in patients with a mortality risk of greater than 25% but also suggest the possibility of increased mortality in patients with lower-risk of death (< 15%). Based upon this, the Surviving Sepsis Campaign guidelines suggest the use of combination therapy for the initial management of septic shock (weak recommendation, low quality of evidence) and suggest against routine combination therapy for sepsis without shock or for bacteremia (weak recommendation, low quality of evidence).

It should be noted, however, that there are significant conflicting data regarding combination therapy in bacteremia, sepsis without shock and septic shock. A randomized, open-label, parallel-group trial of 600 patients with sepsis or septic shock treated with monotherapy or combination therapy did not demonstrate a

change in organ failure or mortality between the two groups [10]. A recent meta-analysis of empirical monotherapy vs combination therapy for adult ICU patients with sepsis showed no difference in mortality or other patient-important outcomes, although the quantity and quality of data was low [11]. Similarly, a meta-analysis of monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis found no difference in mortality but an increase in nephrotoxicity in the combination therapy group [12]. This is consistent with a subsequent study from the Netherlands (which has a low prevalence of antimicrobial resistance) of a short course (median length 2 days) of adjunctive empirical therapy in patients with sepsis and septic shock which found an increased incidence of renal failure but not with improved survival in patients receiving combination therapy [13]. This has led some experts to support using two agents in empiric treatment for septic shock but to de-escalate to monotherapy once susceptibilities become available [14] or to call for more evidence in light of the theoretical benefits of targeted combination therapy but the mix of supporting and non-supporting data and overall insufficient data [15].

Gaps in knowledge/critique of evidence While numerous observational trials have been performed examining combination therapy [16–20], no well-done randomized controlled trial has examined this approach in septic shock patients. Although the most recent Surviving Sepsis guidelines recommend combination therapy for septic shock (and not for sepsis) based upon these available studies for accelerated pathogen clearance [3], the evidence to support this recommendation was assessed as "low quality". The issue of broadening antibiotic coverage was not covered in the Surviving Sepsis guidelines. Guidelines on management of hospital-acquired and ventilator-associated pneumonia suggest combination therapy in some specific settings to assure that the infecting pathogen is sensitive to at least one antibiotic, but the evidence to support this weak recommendation was based upon "low-quality evidence" for ventilator-associated pneumonia and "very low-quality evidence" for hospital-acquired pneumonia [21]. Whether these apply to sepsis for non-pulmonary sources remains to be determined.

Future directions Adequately powered randomized controlled trials should directly test whether combination therapy is beneficial in order to decrease mortality in sepsis and septic shock. These studies should address whether combination therapy is beneficial when used to accelerate pathogen clearance. Separately, studies should be performed to determine whether this approach is beneficial when used to assure that one pathogen is sensitive to a prescribed antibiotic and not when used for synergistic purposes related to pathogen clearance. Since not all combinations would potentially be expected to have equivalent efficacy [22, 23], different antibiotic combinations should be tested to determine if some combinations are more effective than others or more effective than monotherapy. It is critical to note study results may be different based upon local antibiotic resistance patterns and thus must be performed in different settings.

Does optimization of antimicrobial pharmacokinetics and pharmacodynamics impact patient outcomes in sepsis?

What is known Antimicrobial pharmacokinetics (PK) and pharmacodynamics (PD) are important considerations for antibiotic success, which may be particularly relevant in critically ill patients with sepsis and septic shock [24, 25]. The pathophysiologic changes that occur in sepsis can have a major effect on PK by increasing volume of distribution as well as augmenting clearance, resulting in underdosing of antibiotics administered at conventional doses. Further, drug metabolism varies significantly in critically ill patients with sepsis which may result in failure to achieve PD targets for antimicrobials, and hence bacteriological cure. It may also promote emergence of antibiotic resistance.

Gaps in knowledge/critique of evidence Both dosing and timing recommendations for antibiotics are predominantly based on studies performed in the general population which limits their applicability in the clinical setting in patients with sepsis and septic shock where both PK and PD would be expected to be altered [26]. Even though several studies report alterations in PK/PD in patients with septic shock, the impact of this on bacteriological cure and outcome remains to be determined. Alternative approaches to conventional antimicrobial management include the use of extended or continuous administration of some antibiotics and/or higher doses. However, the risk/benefit profiles of these approaches have not been clearly established.

Future directions The factors associated with PK/PD variability to consider in critically ill patients with sepsis and septic shock need to be determined. The impact and cost-effectiveness of incorporating therapeutic drug-monitoring into daily clinical practice to adjust antibiotic dosing in patients with sepsis and septic shock needs to be determined. In addition, studies are necessary to ascertain whether continuous/extended infusion of β-lactams and/or higher doses of antibiotics provide a better bacterial cure and improve outcome. If so, research should determine whether these approaches should be used in all septic patients or only in a subset of selected patients. Ideally, an approach could be utilized in which antibiotic dosing in patients

with sepsis could be determined based on clinical characteristics and source of infection. If this is possible, it leads to the fundamental question about whether it is possible to individualize antibiotic dosing regimens for septic patients.

Should antiviral therapy be administered in the context of viral reactivation in patients with acquired immunosuppression?

What is known The immune response is commonly altered in septic patients [27], and there is growing evidence that critically ill patients may present with a state of acquired immune deficiency (sometimes referred to as immunoparalysis) [28]. Healthy people are frequently asymptomatically infected by viruses that can subsequently persist in a latent state. For instance, cytomegalovirus (CMV) infects approximately 50–80% of otherwise healthy adults, who have lifelong latency in multiple cell types following their initial asymptomatic infection [29]. Several studies have reported reactivation of viruses in critically ill patients that do not have a prior history of being immunocompromised, and this is associated with worse outcomes in critical illness [30, 31]. Notably, in a study of 560 critically ill septic patients, 161 critically-ill non-septic patients and 164 age-matched healthy controls, cumulative viral DNA detection rates in the blood included CMV (24%), Epstein–Barr (53%), herpes simplex (14%), human herpes virus-6 (10%) and TTV (78%) despite these being uncommon in both critically-ill non-septic patients and healthy controls [32]. Notably, 42.7% of septic patients had two or more viruses. These are consistent with studies specifically looking at CMV in the ICU which demonstrate active rates of 17% in non-immunosuppressed patients, mostly occurring between 4 and 12 days after ICU admission [33, 34].

A recent trial of 160 CMV-positive patients with sepsis or trauma randomized participants to receive ganciclovir or placebo. Despite lower levels of CMV reactivation in the treatment group, no difference was noted in the primary outcome (IL-6 levels) although ventilator free days were higher in the treatment group [35]. In contrast, a single center trial of 124 CMV-seropositive patients undergoing mechanical ventilation randomized patients to receive anti-CMV prophylaxis with valacyclovir or low-dose valganciclovir. While valacyclovir decreased viral reactivation in the blood (12 patients vs. 2 patients), this finding was associated with an increase in 28-day mortality in patients receiving valacyclovir (41.2% in treatment arm vs. 13.5% mortality in control arm) [36].

Gaps in knowledge/critique of evidence Viral reactivation has been shown to be associated with a worse outcome but it is unclear whether the increased risk of death is related to the underlying condition or whether the viral reactivation itself contributes to the increased risk of death. The role—if any—of either prophylaxis or treatment of CMV reactivation is not clear, being limited to small studies. Further, the role of prophylaxis or treatment of viral infections outside of CMV is understood even less.

Future directions Randomized controlled trials should be performed to delineate the role (if any) of prophylaxis against viral reactivation. Similar trials should be performed to determine if treatment, once viral reactivation occurs, confers any benefit in altering mortality and/or other patient-centric outcomes. If either strategy is beneficial, it needs to be clarified whether prophylaxis or treatment is beneficial in all septic patients or only in a subset. Further, studies need to delineate whether specific viruses (CMV, EBV, HSV, HHV-6, TTV) carry therapeutic or prognostic significance. These studies should answer the question whether viral reactivation plays a role in mediating poor outcomes or is simply a marker of worse outcomes.

Should rapid diagnostic tests be implemented in clinical practice?

What is known Sepsis is a time-sensitive condition, with delays in either diagnosis or therapy leading to increased mortality. Faster diagnosis of sepsis could potentially reduce mortality, shorten length of stay, and lower hospital costs [37, 38]. However, diagnosis of sepsis relies upon a clinician suspecting infection without the actual ability to diagnose infection in real time. A significant number of patients with sepsis never have positive cultures. In addition, even in patients whose cultures will ultimately be positive, there is a time lag of hours to days between when the sample is sent to when the positive result is obtained. Further, outside of the potential utility of biomarkers such as procalcitonin, there is little available to the clinician to determine if the infection has resolved. The inability to rapidly diagnose infection and/or to determine when the infection has cleared can lead to widespread usage of broad spectrum antibiotics [39]. Notably, despite advances in the technology available to treat septic patients, culturing techniques used for identifying infection have not changed substantially over a number of decades. Numerous rapid diagnostic tests have been tested in patients for the identification of infection. Further, numerous biomarkers have been tested for the identification or prognostication of sepsis (covered elsewhere in this manuscript).

Gaps in knowledge/critique of evidence Identification of the causative organism has traditionally involved phenotypic analysis of organisms isolated from positive cultures. However, this process can take days, during which time patients may be treated with broad-spectrum

antibiotics until positive pathogen identification becomes available (which may never happen considering that many septic patients are culture negative). In addition, it is sometimes difficult to obtain samples. For instance, sputum is not always available in septic patients with pneumonia who are not intubated, and peritoneal fluid is not always accessible in septic patients with peritonitis. Faster and more accurate pathogen identification is therefore critical [40, 41]. When a culture is flagged as positive a gram stain is performed that can potentially provide information about the type of organism responsible for the infection; however, this does not provide an acceptable level of accuracy to guide therapy. Instead, tailored therapeutic intervention relies on identification of species, which can take days using conventional techniques, and the antibiotic resistance profile will typically be available only 1–2 days after that. Further, detection of fungi, viruses, and anaerobic bacteria can be more challenging than detecting aerobic bacteria, both in terms of timing and sensitivity. Several methods to detect the implicated pathogen (bacterial DNA detection, syndromic PCR) and detection of resistant organisms and/or rapid antibiogram have recently developed [42–45]. Unfortunately, none of these techniques has been widely adopted due to a combination of factors including (but not limited to) cost, logistics and accuracy concerns.

Future directions Future research should evaluate whether existing rapid diagnostic tests facilitate diagnosis and should be implemented in clinical practice. If so, studies need to determine which techniques and/or methods are superior or if further optimization is required, which may require both technological advances and examination of test accuracy across a variety of resource settings. Importantly, the role of rapid diagnostic tests in antibiotic stewardship (when to start, how broad, when to de-escalate, when to stop) needs to be examined. Further, although it is logical to believe that rapid diagnostic tests could potentially change patient outcomes, this assumption should be formally tested. Finally, assessing the immune system and performing rapid diagnostic tests might potentially help identify both the infecting organism and the dysregulated host response simultaneously, and an integrative approach examining both microbe and host may yield critical insights that assaying each in isolation might miss.

Fluids and vasopressors

What are ideal endpoints for volume resuscitation and how should volume resuscitation be titrated?

What is known The administration of intravenous fluids to improve circulation, perfusion, and oxygen delivery is a fundamental principle in sepsis management [46]. However, the potential benefits of administering fluid must be balanced against the potential for harm due to the accumulation of fluid, such as, pulmonary edema, abdominal compartment syndrome, and tissue edema. Current recommendations from the Surviving Sepsis Campaign suggest resuscitating patients with sepsis-induced hypoperfusion with at least 30 ml/kg of IV crystalloid within the first 3 h [3]. The Surviving Sepsis bundles have been associated with improved survival in numerous large-scale studies [4, 6, 47], although the specific importance of each individual component of the bundle is unclear. It should be noted that while more rapid completion of the 3 h bundle and rapid administration of antibiotics was associated with improved outcome in a study of nearly 50,000 patients, a longer time to completion of initial fluid bolus was not associated with a change in mortality [6]. Further, the amount of fluid administered was not associated with survival differences in observational and randomized studies of early goal directed therapy [48]. Also, an early resuscitation protocol including intravenous fluids, vasopressors, blood transfusion and invasive monitoring was associated with increased mortality compared to usual care in patients with sepsis (mostly HIV) and hypotension in a developing country [49].

The fundamental reasoning for administering fluid is to improve tissue perfusion by increasing cardiac output [50]. Traditional approaches to titrating fluid administration have been based on static measures of preload [51]. Dynamic indices of preload may better predict the response to fluids but still remain underused [52]. However, there are instances where a patient will not improve despite the administration of fluids. Identifying robust clinical parameters that distinguish patients likely to positively respond to a fluid bolus from those unlikely to respond is an essential need in sepsis care. One important caveat to mention is that while there is inherent value in determining which patients will respond to fluid boluses, it is unclear whether this will result in improved outcomes.

Gaps in knowledge/critique of evidence Current approaches to determine fluid responsiveness include the application of empiric fluid boluses, static measurements, and dynamic markers. The empiric administration of a fluid bolus to determine fluid responsiveness is inherently troublesome since a substantial number of patients will not respond, potentiating harm. The worst case scenario is when this empiric administration is done without any measurement of effectiveness and tolerance which can often lead to repeat administration when the problem triggering fluid administration persists.

Static measures involve the placement of venous catheters to facilitate the measurement of central venous pressure (CVP) and pulmonary capillary occluded pressure (PAOP) and evaluate baseline and incremental changes

in pressure following fluid administration. However, fluid responsiveness on the basis of CVP has not consistently demonstrated validity as a measure of fluid responsiveness [53]. Dynamic measures include a variety of techniques to assess the change in cardiac output in response to transient changes in preload induced by ventilation or an external maneuver, prior to fluid administration. Common types of dynamic measures used in clinical practice include passive leg raise (PLR) maneuver, respiratory variation, pulse pressure variation (PPV), and stroke volume variation (SVV) [54]. However, variations in respiratory patterns or pulse pressure and stroke volume can be difficult to interpret in spontaneously breathing patients. PLR is most useful when a rapid-response cardiac output monitoring is available [55], but still requires rigorous investigation and testing.

Importantly, the determination of triggers to administer fluids after initial resuscitation as well as triggers to stop fluid resuscitation remain poorly understood. While there is a significant literature evaluating many of these methods in the peri-operative setting and in non-selected critical care patients, there is a paucity of literature comparing the various methods for assessing fluid responsiveness in patients with sepsis/septic shock. In these patients the validity of these tests may be impaired due to the impact of vasoplegia, use of low tidal volume ventilation and presence of respiratory movements or increased abdominal pressure. Furthermore, application and translation of these findings across all types of clinical settings is necessary. This includes developed countries in settings where minimal monitoring devices can be implemented (i.e. hospital wards) as well as low- and middle-income countries which account for a majority of all cases of sepsis worldwide. Clinical utility of tests for fluid responsiveness need to be reproducible and applicable in resource-limited settings.

Future directions While great progress has been made in the clinical investigation of fluid resuscitation, pressing uncertainties remain leading to the following core questions: (a) do ideal clinical parameters and endpoints for volume resuscitation exist; (b) how should volume resuscitation be titrated; (c) what is the optimal dose of initial volume bolus administration; and (d) how should the approach for volume resuscitation be modified in resource-limited settings?

In the course of routine clinical care, physiological parameters are explicitly framed to direct the administration of any therapy (e.g. anti-hypertensives for the treatment of hypertension). In contrast, ideal physiological parameters to outline therapeutic endpoints for fluid resuscitation, titration, and amount of volume are largely unknown and remain ambiguous. Traditional approaches of 30 ml/kg of initial volume bolus were founded over a decade ago, and dictate a "one size fits all" strategy of initial fluid administration [56]. While there is benefit to a standardized approach to initial fluid resuscitation (especially for clinicians relatively inexperienced in the management of septic patients), the ideal approach would be personalized pending on individual patient need.

Subsequent fluid administration is even more complicated and is often driven by various approaches The need to identify the optimal measures of fluid responsiveness directly influences the clinician's ability to determine if further volume administration may be beneficial and if the patient is likely to positively respond to fluids, and how therapy should be titrated (which amount/speed of infusion/stopping rules). Randomized, controlled trials are needed to determine if greater precision is possible to determine how much fluid can be administered as a single dose for a given patient. Additionally, these questions and approaches should be tested to identify the optimal approach in resource-limited settings. Finally, studies evaluating clinical endpoints for resuscitation should be tested in a pragmatic design to promote diffusion of findings and rapid uptake into clinical practice, particularly in resource-limited settings.

What is the optimal fluid for sepsis resuscitation?

What is known Broadly stated, large randomized, controlled, multicenter trials have found no significant difference between albumin and crystalloids. The Saline versus Albumin Fluid Evaluation (SAFE) study found no difference in 28-day mortality for patients randomized to 0.9% normal saline or 4% albumin, although there was a trend towards improved outcomes in the study for patients with sepsis in a post hoc subgroup analysis [57]. Mortality was also not different between patients receiving 20% albumin or crystalloid in a large randomized trial in patients with sepsis or septic shock (ALBIOS trial) [58]. However, while the overall study did not show a difference in outcome, subgroup analysis showed improved mortality in patients with septic shock. Multiple meta-analyses have been performed comparing albumin to crystalloid, although different populations have made combining the data challenging [59]. Together, these have led to a weak recommendation (based upon low quality evidence) in the Surviving Sepsis Campaign for using albumin in addition to crystalloids for both initial resuscitation and subsequent intravascular volume replacement in patients with both sepsis and septic shock who require substantial amounts of crystalloid [3]. Within the context of the broader categories of crystalloids and colloids, there exist distinctions between individual fluid choices [60, 61]. Hydroxyethyl starch should not be used on the basis of the increased risk for acute kidney injury

and need for renal replacement therapy, in addition to increased mortality in many meta-analyses [62–65].

There is developing interest in administering crystalloids with a balanced ion content to reduce the chloride load observed with 0.9% normal saline [66]. Crystalloid solutions, such as, Ringer's lactate and PlasmaLyte, have been studied with varying results [67]. Lactate-based chloride-free solutions have been developed and can improve cardiac output and blood pressure while achieving a negative fluid balance [68]. While numerous smaller studies have demonstrated benefit in balanced crystalloids, a randomized controlled comparing 0.9% normal saline to PlasmaLyte did not reduce the risk of acute kidney injury [69]. However, while this study is widely quoted, the majority of the patients were admitted following elective surgery, had relatively few co-morbidities, received a relatively small amount of fluid, were not septic, and the overall mortality was low. As such, the relevance of this study to septic patients is unclear. Recently, two large randomized controlled trials compared balanced crystalloids to 0.9% normal saline in 15,802 critically ill patients from 5 ICUs and 13,347 non-critically ill emergency department patients who were subsequently hospitalized outside of the ICU [70, 71]. In critically ill patients, balanced crystalloids resulted in a statistically significant 1.1% decrease in the composite outcome of death from any cause, new renal-replacement therapy or persistent renal dysfunction. While balanced crystalloids did not change the primary outcome of hospital free days in non-critically ill patients, they were associated with a statistically significant 0.9% decrease in the composite outcomes of major adverse kidney events seen in critically ill patients. Although a subgroup analysis showed a larger decrease (5.1%) in composite outcome in septic patients given balanced crystalloids, it is important to note that patients with sepsis or septic shock represented less than 15% of the ICU patients in this study [70]. Further, the percent of septic patients was not reported in the study on non-critically ill patients [71]. As such the applicability of these results to septic patients (who often require a greater amount of fluids, and suffer from a higher incidence of kidney dysfunction and have a higher risk of death) remains to be determined.

Gaps in knowledge/critique of evidence Existing trials have not sufficiently evaluated fluid administration in the full continuum of acute sepsis, including initial fluid resuscitation, subgroups of patients, and adequately controlling for bias. While the detrimental effects of small amounts of any given fluid are often negligible, significant adverse effects may arise when large amounts are administered. Many of the trials that have been conducted have administered very limited amount of fluids so that these concluded that no difference was detected. Furthermore, as the burden of sepsis is better recognized, evaluating fluid types that are widely available around the world is necessary.

Future directions The choice of fluid in early sepsis resuscitation is still largely unknown and needs to be delineated. Further, the choice of fluid once initial resuscitation has been completed is equally unclear. Despite numerous studies, the role of colloids is still unclear including when to use, how much to use, and type to use. Finally, trials distinguishing between balanced crystalloids and normal saline are necessary but these should mimic the behavior of clinicians and take into account chloride measurements and potentially stopping once hyperchloremia develops. Given the heterogeneity of sepsis etiology, subgroups of sepsis need to be further evaluated to determine if there are specific groups in which type of fluid impacts outcomes. Finally, fluid choice in resource-limited areas has not been fully described, and pragmatically designed trials are required to investigate optimal fluids in these settings.

What is the optimal approach to selection, dose titration, and escalation of vasopressor therapy?

What is known Norepinephrine has been demonstrated to be a superior vasopressor option when compared to dopamine in a broad group of patients with shock [72]. Epinephrine is also a suitable substitute as a vasopressor when inotropy is also required (similar to a combination of a norepinephrine and dobutamine). As a non-catecholamine vasopressor, vasopressin has been demonstrated to be safe as an adjunct agent to norepinephrine and to potentially improve outcome in a subgroup of patients with less severe septic shock [73]. Of note, vasopressin as a primary agent has been compared to norepinephrine, yielding no difference with regards to acute kidney injury and failing to confirm the beneficial effects in patients with less severe shock [74]. More recently, angiotensin II has demonstrated efficacy in raising mean arterial pressure (MAP) but outcome data are still lacking [75]. In contrast, non-selective inhibition of nitric oxide synthase has been shown to increase mortality [76], highlighting that evaluation of vasopressors should not be based solely on its hemodynamic effects. Finally, a higher MAP target has not been shown to be beneficial in patients in septic shock, although in a subgroup of patients with severe baseline hypertension, targeting a higher MAP is associated with less need for renal replacement therapy [77].

Gaps in knowledge/critique of evidence Studies designed over the past two decades of septic shock research have varied in design and in endpoints, making it difficult to consistently evaluate different vasopressor agents. Studies have used varying doses of vasopressor agents, resuscitation strategies, clinical endpoints, and therapeutic

escalation strategies. Trials evaluating the effects of epinephrine were markedly underpowered. Admittedly, none of these showed beneficial effects of epinephrine, but it remains to be determined whether some subgroups of patients may benefit from epinephrine usage. A common framework for how vasopressors should be studied is lacking. Trials evaluating higher versus lower MAP were always above target in the low target groups (65 mmHg). Hence, the current recommendations supporting using pressors to maintain MAP at 65 mmHg are only supported by observational data.

Future directions Essential questions remain regarding vasopressor selection, escalation of therapy, sequencing of vasopressor agents, combination regimens, and dose titration. Using the broader categories of fluid choices (crystalloids and colloids) as an analogy, a therapeutic approach comparing a catecholamine (e.g. norepinephrine) to a non-catecholamine (e.g. vasopressin, angiotensin II) to raise MAP and improve survival is necessary. Similarly, the role of epinephrine as a second line agent needs to be evaluated. Further, while angiotensin II has recently been shown to effectively increase blood pressure in patients with vasodilatory shock that do not respond to high doses of conventional pressors, the indications for this new agent remain to be determined as do its effect on outcomes. Defining an acceptable dose range of vasopressors for which to escalate therapy vs. initiate a second agent is also necessary. To accomplish this effectively requires rigorous investigation into how vasopressors are dosed and titrated. Finally, subgroups of patients should be evaluated (heart failure, essential hypertension), given the predilection of some patients to suffer adverse events of hypotension as well as those resulting from vasopressor therapy (arrhythmias or acute kidney injury).

Adjunctive therapy

Can targeted/personalized/precision medicine approaches determine which therapies will work for which patients at which times?

What is known In light of the individual variability of septic patients, traditional clinical trial results currently have an inability to predict the response to an intervention at the level of an individual. Similarly, clinical practice guidelines are based upon a composite of overall best practice for the greatest number of patients. This does not account for individual differences as an intervention in a trial that showed overall benefit could potentially be of no benefit or harm to an individual participating, whereas an intervention in a trial that showed no benefit could potentially be beneficial to a subgroup of participating patients. The pathophysiology of sepsis is a complex and dynamic process that originates from the host response to infection and varies according to (at a minimum) the genetic predisposition, immune status, age and comorbid conditions of the host, the type of pathogen and the site and extent of infection. Recent advance in omics (genomics, epigenomics, transcriptomics, proteomics, metabolomics, pharmacogenomics, microbiomics) have the potential to revolutionize care by assaying the state of an individual [78, 79]. Individual insights need not be confined to "omics"-based data, however, as important insights can be drawn from easily interpretable clinical information and by use of big data approaches that allow insight from information accessible within the ICU that might not be able to be processed by a bedside provider [80].

Gaps in knowledge/critique of evidence At present, precision medicine for sepsis remains a vision in the distance [81, 82]. There are considerable amounts of data characterizing sepsis patients according to a single biomarker, but there are limited data that broadly phenotype sepsis patients and no application of these data to influence patient care [83]. An example of an early attempt was the MONARCS trial, where sepsis patients with IL-6 levels >1000 pg/mL were targeted for treatment with an anti-TNF monoclonal antibody [84]. Similarly, attempts at targeting corticosteroid therapy have not been successfully reproduced, yet corticosteroids are used frequently in patients with septic shock [85, 86]. Precision medicine may also rely on clinical signs. As an example, an ideal trial on inotropic agent for treating the consequences of sepsis-associated myocardial depression should include patients with signs of tissue hypoperfusion associated with a low or inadequate cardiac output related to an impairment in contractility. This is a different approach from a recent trial design that included patients in shock with minimal (if any) assessment of cardiac output and cardiac function [87].

Future directions The first step toward precision medicine in sepsis is characterizing the clinical and biological heterogeneity within the syndrome. As one example, the immune response in septic patients ranges from an exuberant pro-inflammatory cascade to a profoundly immunosuppressed phenotype, yet there is currently an inability to accurately phenotype patients at the bedside to know where an individual patient lies on the immune response spectrum. An approach that has potential immediate clinical applicability is targeting precision use of corticosteroids, to determine the right patient, the right time and the right dose, as well as monitoring for the right response to therapy.

On a longer horizon, the development of novel methods to rapidly immunophenotype patients could enable the targeted application of therapies and

monitoring of treatment response. Further, the use of both omics and big data to understand the individual response, combined potentially with the use of in silico modeling, has the potential to revolutionize the management of sepsis.

Determine the efficacy of "blood purification" therapies such as endotoxin absorbers, cytokine absorbers and plasmapheresis

What is known A number of studies address this diverse area, whose common endpoint is the elimination of bloodstream substances that are felt to be harmful. Most of the studies are relatively small, often have methodologic issues and often concentrate on the elimination of mediators as the outcome of interest rather than a clinical outcome such as mortality. A 2013 meta-analysis of 16 trials concluded that blood purification decreased mortality in sepsis compared to no blood purification. However, these results were driven mainly by hemoperfusion and plasma exchange, and pooling of all trials of blood purification for treatment of sepsis was no longer associated with lower mortality after excluding trials using polymyxin B hemoperfusion [88]. There is also a negative study pending publication using polymyxin B hemoperfusion presented at ESICM LIVES 2016 [89]. Observational data (registries) support the use of cytokine hemoadsorption but there are no randomized data at this stage.

Gaps in knowledge/critique of evidence A major issue is the heterogeneity of the techniques, as results obtained with one technique may not apply to the other techniques. The most commonly used techniques are cytokine hemoadsorption and polymyxin-b hemoperfusion, with polymyxin-b hemoperfusion being widely used in Asian countries and cytokine hemoadsorption being common in Germany. However, there are numerous knowledge gaps including characterizing what can be expected from these techniques (short term hemodynamic vs modulation of host response), characterization of the potential adverse effects (optimization of anticoagulation, pharmacokinetics of antibiotics), characterization of all molecules removed, and defining which patients (if any) may potentially benefit from these techniques and at which time during the evolution of their sepsis.

Future directions There is a clear necessity for large, well designed, definitive studies in patients with sepsis and/or septic shock, especially since blood purification strategies are currently being used in highly selective places around the world. There is concern that a large scale trial including unselected patients would more than likely be negative, exposing patients to potential side effects of extracorporeal techniques without expected benefits. The challenge to design trials include finding the correct patient population as well as incorporating the potential financial consequences, as these systems are costly.

What is the ideal method of delivering nutrition support, including route, timing and composition of nutrition support, and whether this varies by hemodynamic status?

What is known Variable results have been reported from various studies with various methodologies [90–94]. Despite nutrition support being available for many years, there is limited conclusive evidence favoring any aspect of its use. Prior studies have failed to demonstrate the efficacy of early parenteral nutrition in critically ill patients, and the most recent studies suggest early feeding, whether enteral or parenteral, may be equivalent [95]. Comparing early full enteral nutrition with limited caloric intake ("trophic feeds") one large study found only small differences in gastrointestinal intolerance without evidence of harm or benefit, whereas a smaller, more recent retrospective study on patients in septic shock suggested that trophic feeds may reduce the duration of mechanical ventilation and length of stay in the ICU [93, 96]. There are similar controversies and inconsistencies in the literature regarding micronutrient supplementation, immunonutrition, assessing feeding tolerance, feeding patients in the presence of shock, and goals of nutrition support in sepsis [97, 98].

Gaps in knowledge/critique of evidence Questions regarding timing (including when to initiate and when to stop), composition, dose and route of nutritional support therapy in sepsis are incompletely understood, as most studies have been carried out in a general critical care cohort, and not specifically in patients with sepsis/septic shock. Moreover, many of the studies have high risk of bias and are underpowered. Further, several basic aspects of enteral nutrition support remain uncertain. It is unclear if the proper goal of providing enteral nutrition is to reach a certain caloric goal or if there a superior target. There is also significant controversy about whether feeding tolerance should be measured using gastric residual volume or other indicators and whether this is impacted by type of patient (surgical vs. non-surgical). There is also a lack of clarity regarding whether nutrition formulas need to be altered in sepsis, such as with micronutrient supplementation or immunonutrition formulas. For patients with septic shock, it remains to be determined at what dose of vasopressors enteral nutrition can be provided (and if type of vasopressor impacts this), if there is a maximum tolerated dose during shock, and if there is a benefit to trophic enteral feeding (with or without parenteral nutrition) while on pressors. Finally, it is unclear how chronic comorbidities (chronic kidney

disease, diabetes mellitus, chronic respiratory failure, obesity, etc.) alter nutrition needs in sepsis.

Future directions Research should focus individually on each variable as best as practicable. A first step may be to start with timing of nutrition. Later studies can examine both dose and composition (including immunonutrition). Studies should be performed in patients with sepsis and septic shock to determine the role of hemodynamic status on each factor.

What is the role of lung protective ventilation in septic patients without ARDS?

What is known Lung protective ventilation (LPV) has been proven effective for reducing mortality and reducing the duration of mechanical ventilation in patients with ARDS [99] although aggressive recruitment maneuvers and PEEP titration have been associated with increased mortality in ARDS [100]. Observational studies suggest reductions in the development of ARDS with LPV use in patients *at risk for* ARDS but who had not yet developed the syndrome [101]. Two meta-analyses suggest that use of LPV in patients without ARDS reduces the duration of mechanical ventilation, the risk of pulmonary infection and the duration of hospitalization [102, 103]. Given the frequency of respiratory failure in sepsis, with consequent high risk for developing ARDS and its attendant complications of prolonged mechanical ventilation and mortality, optimizing the approach to mechanical ventilation could save thousands of lives and reduce healthcare costs through reductions in mechanical ventilation and ICU stay.

Gaps in knowledge/critique of evidence Current evidence is observational and is not limited to septic patients. Controlled trials in related fields such as perioperative respiratory management demonstrate benefits for the use of LPV in patients without ARDS [104]; however, their applicability to septic patients is, as yet, undetermined. The PReVENT study is currently ongoing to examine the role of LPV in critically ill adult patients for improving the number of ventilator-free days [105].

Future directions Conducting a definitive clinical trial in patients with sepsis (the most common cause of ARDS) is of significant importance.

Scoring/identification

What information identifies organ dysfunction?

What is known Clinical criteria for sepsis in the Sepsis 3 definition are based on a model where the outcome variables are either mortality or a composite of mortality and increased length of ICU stay [1, 106, 107]. The Sequential [Sepsis-related] Organ Failure Assessment (SOFA) and quick SOFA (qSOFA) are scoring systems that use clinical data as surrogates for organ dysfunction [108]. These clinical constructs are based on objective measurements that are easily obtained and are linked to outcomes that can be the result of clinical decision making (i.e., the decision to discharge from the ICU or to withdraw life-sustaining therapies). Relatively little is known, however, about the pathobiology of dysfunction in individual organ systems that is associated with these outcomes. Clinical identification is based largely on surrogates (e.g., serum creatinine, serum bilirubin, blood pressure, PaO_2/FiO_2 ratio, Glasgow coma scale, platelet count, respiratory rate). In contrast, a diagnosis such as myocardial infarction correlates serum markers (troponins, creatinine kinase subgroups) to functional studies (wall shortening on echocardiography, changes in electrocardiogram pattern) and anatomy (angiography, histology).

Gaps in knowledge/critique of the evidence Organ dysfunction cannot currently be identified with the degree of precision needed to create a diagnostic gold standard for sepsis similar to that which exists for other diseases. Absent such a standard, clinical criteria must be used to construct predictive models for sepsis. In the current state, these criteria are limited in their ability to differentiate a septic patient from a patient with other disorders. In addition, current predictive models are based on outcomes (mortality, length of stay) that themselves may be biased by subjective clinical decisions.

Future directions Studies that address the lack of gold standards for sepsis-associated organ dysfunction are needed. This will likely require translation of animal models of organ dysfunction or human markers with specific indicators of organ function. Some possible examples include myocardial wall motion on imaging, renal tubular ion pump function, hepatic synthetic pathways, real-time assessment of host immune status, histopathology, and omics-based expression patterns. The short-term translational goal will be to correlate functional findings with existing clinical markers. Ideally multiple independent assessments of organ function would be used to try to provide a comprehensive assessment of whole organ function. Gold standards for each organ would correlate with available clinical findings (laboratory, imaging, functional assessment) which would then be correlated with clinical outcomes. Clinical criteria for sepsis definitions could then be adapted to provide more precise identification of organ dysfunction. Long-term, markers of organ dysfunction that either do not exist currently or exist only in the research domain would ideally make the diagnosis of organ dysfunction more mechanistic and precise. Finally, although it is reasonable to assume that prevention or early treatment of organ dysfunction improves outcome in sepsis, clinical studies should test this supposition.

How can we screen for sepsis in varied settings?

What is known Sepsis is managed in a variety of settings, including high, low and middle-income countries, differently-equipped facilities and in and out of hospital, including pre-hospital transport. Absent a diagnostic gold standard, screening tools must either predict important outcomes or correlate with the development of a recognizable entity, as a generally agreed clinical picture of sepsis. The need to avoid missing at-risk patients is an important consideration, especially in environments where a missed opportunity to intervene may have a strong effect on outcomes. Over-triage of patients who may not have sepsis or progress to develop sepsis risks wasting resources and exposing patients to the risks of unnecessary interventional therapies. At the same time, under-triage of patients runs the risk of late identification, which is associated with increased risk of death. Both of these issues are likely exacerbated in resource-limited environments. The purpose of a good screening tool is to identify populations at risk and compel further assessment and treatment while ideally excluding those not at risk.

Gaps in knowledge/critique of the evidence Although the clinical criteria in Sepsis 3 were developed using large derivation and validation cohorts, all of the data in the primary publication are from high-income countries [106, 107]. Subsequent studies appear to validate the criteria in both low-middle and developing countries [109–111], although this is relatively limited in scope. There are also two large prospective evaluations of the predictive model in the literature from the United States and Australia [112, 113]. In addition, goals for a screening tool may vary by setting, as high-resource environments might potentially trade under-triage for better accuracy, whereas low-resource environments might benefit from initial over-triage, so as not to miss high-risk cases. Finally, the purpose of the screen—to compel further assessment and treatment—has not been adequately studied.

Future directions Existing models for sepsis screening should be refined. Further, there should not be an assumption that all environments are the same and that a "one size fits all" screening tool will work the same, independent of location. As such, the efficacy of screening tools should be tested in different environments. Ideally, this would take the form of prospective studies linked to clinically meaningful outcomes, although numerous study designs could potentially yield important information. These studies should look at triggered clinical actions which could be diagnostic or therapeutic, and whose correlation to a variety of clinically important outcomes would be determined. Research should characterize construct or predictive validity of any screening tool including sensitivity, specificity, positive predictive value and negative predictive value. Studies should consider a variety of clinically important outcomes.

How do we identify septic shock?

What is known Septic shock occurs in the setting of a physiologic state of hypoperfusion. Sepsis 3 defines septic shock as "a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality [1]." Based upon a large database analysis and a Delphi process, the Sepsis 3 taskforce identified clinical criteria for septic shock as (a) hypotension, (b) requiring vasopressors and (c) a lactate >2 [107]. While lactate typically correlates with perfusion abnormalities, it may also be associated with abnormal metabolism. Further, while Sepsis 3 (and previously Sepsis 1 and 2) includes definitions without recommendations for management, the Surviving Sepsis Campaign Guidelines give differential antibiotic recommendations for sepsis as compared to septic shock, often based on very low certainty of evidence [3].

Gaps in knowledge/critique of evidence Consensus as to what defines shock is lacking. Although many clinicians characterize shock by perfusion indices, this does not provide a clear definition based on mechanisms. Further, the clinical criteria in Sepsis 3, while based upon large database analysis, were not unanimously agreed upon by the taskforce. Although there was a clearly articulated rationale for why the clinical criteria for septic shock required hypotension, vasopressors and an elevated lactate (significantly higher mortality than any of these in isolation), many in the community continue to believe that shock should be defined as hypotension/vasopressors OR elevated lactate, rather than AND. In addition, many locations throughout the world cannot measure lactate, which leads to the question of how one identifies septic shock at the bedside if a clinician cannot measure lactate. Further, there is limited evidence comparing the metabolic and circulatory abnormalities between sepsis and septic shock, and it remains unsettled whether septic shock is truly a unique entity or simply a manifestation of a greater severity of sepsis.

Future directions Research should address the fundamental question of whether septic shock is a disorder that is distinct from sepsis. If it is, efforts should address proxies for septic shock that have predictive validity for important outcomes or construct validity for a helpful clinical entity. These proxies could be correlated to clinical presentation in an effort to identify a unique group of high risk patients. Models could be created from large databases and then prospectively validated in larger groups of patients. The impacts for diagnosis, treatment and outcomes should be prospectively assessed.

Importantly, investigation should address the question of whether septic shock needs to be treated differently than sepsis outside of the institution of vasopressors. Investigation should not rely on an outcome (mortality) that is both the independent variable (used when creating the definitions to differentiate the two entities) and the dependent variable (the most common outcome used in clinical intervention studies). Finally, the clinical criteria for septic shock in Sepsis 3 should be prospectively validated.

What in-hospital clinical information is associated with important outcomes in septic patients?

What is known Clinical criteria used to identify sepsis in patients with suspected infection are derived from the association between mortality, length of ICU stay, and a discharge diagnosis of sepsis. The construct validity is based on limited, but clinically available, criteria (SOFA or qSOFA score ≥ 2, suspected infection) and validated to a few outcomes. At the bedside, clinicians draw on a larger collection of data to make diagnostic and therapeutic decisions. Ultimately, practitioners make clinical decisions, such as limiting life-sustaining therapies and deciding to transfer patients into or out from an ICU, based on an impression of prognosis.

Gaps in knowledge/critique of evidence The new Sepsis 3 definition has substantially improved construct validity for the concept of sepsis [114]. SOFA is an older tool that predicts mortality in patient populations, although some elements of the SOFA score are outdated (such as "renal dose" dopamine). In addition, qSOFA has fairly robust validity in predicting mortality and prolonged stay in patients prior to ICU admission (although its accuracy is lower in the ICU) [112, 115–117]. However, both mortality and increased length of ICU stay are themselves influenced by clinical decision making. Many important clinical outcomes, such as cognitive dysfunction and lasting organ dysfunctions, have not been studied. It is also unclear if the variables or specific elements in SOFA need updating. The pathobiology of many (if not most) adverse outcomes in the ICU is not described.

Future directions Research is needed both in improving which clinical information is utilized and in assessing patient-centric outcomes beyond mortality and length of ICU stay (understanding that these continue to be critically important outcomes). This is far reaching as it requires enhanced understanding of what is most important out of a massive amount of data readily available to the ICU team (essentially everything in the electronic medical record), data that exist but might not be readily available (heart rate variability as an example) and data that are currently not available (a moment by moment assessment of a patient's immune status). Further, it requires a conversation between clinicians and patients/families as to what outcomes are most important. Answering the two components of this research question will therefore require studies ranging from (but not limited to) (a) animal modeling, (b) new study designs, (c) big data approaches, (d) creation of new technologies, and (e) survey and face-to-face meetings to understand what outcomes are most valued. Measures should be assessed individually and as multiple, interactive variables, to establish relationships between different organ dysfunctions.

Administration/epidemiology

Which is the optimal model of delivering sepsis care?

What is known The way in which ICUs and their larger hospitals and healthcare systems are organized and managed affects quality and efficiency in sepsis care. Further, both early recognition and early intervention in sepsis saves lives. Performance improvement efforts for sepsis are associated with improved patient outcomes. An example of this is the Surviving Sepsis Campaign bundles, in which rapid antibiotic administration and fluid resuscitation are associated with lower mortality [4, 118–121]. Sepsis performance improvement programs should optimally have multiprofessional representation (physicians, nurses, advanced practice providers, pharmacists, respiratory therapists, nutrition support specialists, administrators). Successful programs should include protocol development and implementation, targeted metrics to be evaluated, data collection, and ongoing feedback to facilitate continuous performance improvement. Ideally, sepsis performance improvement programs should be sustained over time with repeated assessment of key metrics and additional intervention if there is a failure to "hold the gain". Despite many success stories, many ICUs, hospitals and healthcare systems have been slow to adopt recommended sepsis protocols or initiate quality improvement programs because of a myriad of implementation challenges and/or financial concerns.

Gaps in knowledge/critique of evidence Although both bundles (intended for quality improvement) and guidelines (intended to help guide practice) are based on the best available evidence, they are frequently not supported by high-quality evidence. While it is known that adaptation of process of care to different health care systems around the globe is highly variable, there is a lack of understanding both in the extent of this variability and its causes. Within bundles, even if beneficial in aggregate, this does not mean that each component has equivalent efficacy (or any efficacy) and whether other critical elements are missing entirely that would potentially change outcome.

Future directions Research towards understanding which systems of sepsis screening and care delivery are

most beneficial and cost-effective in a wide variety of patient care environments is critical. This should not be limited to the ICU but include the emergency department and the wards (and potentially both pre-hospital emergency care and outpatient facilities for sepsis screening as well) [122, 123]. These can be intra-location delivery systems (i.e. ICU-specific, ED-specific), intra-hospital, intra-health care system or regionalized (such as in trauma care in many countries). Methods of determining and then tracking optimal communication, transitions of care, and multidisciplinary coordination of care will likely be critical to this effort. Determining the best tool to detect the at-risk patient with optimal sensitivity and specificity is equally important. Finally, research should attempt to determine the relative importance of each bundle component and elements should be added, deleted or modified based upon these results.

Which is the epidemiology of sepsis susceptibility and response to treatment?

What is known Sepsis is a heterogeneous syndrome. The phenotype of sepsis in an individualized patient is influenced by both specifics of the infectious process and the host response of an individual patient. Different infections will impact the host differentially, and even within a single organism, different virulence factors will induce distinct responses. The host response is equally variable, and different genetic, epigenetic, and cellular/subcellular factors lead patients to respond very differently to the identical therapy [124–130].

Gaps in knowledge/critique of evidence Although Sepsis 3 is an intellectual advance, it continues to be non-specific, and does not make distinctions between either type of infection or host response [1, 2, 131–134]. An urgent need thus exists to better characterize different subgroups of sepsis, assuming they exist (which is likely). The field of precision medicine as it relates to sepsis is still in its infancy, so an ability to characterize patients based on their biological profile rather than clinical criteria alone is not currently possible at the bedside.

Future directions Research should improve the epidemiological information of sepsis in different subgroup of patients. In the short-term, this might be based upon factors that are currently identifiable such as transplant, oncohematological, elderly, etc. In the longer term, this should be more individualized and more biological in nature. Factors that require tailoring of therapy should be assayed. This should include both pathogen factors and host factors (phenotypes, endotypes, omics, real time assessment of immune function). Ideally, this would allow clinicians to prophylax against sepsis as well as treat the syndrome in an individualized manner.

It is possible to stratify the risk of sepsis based on biomarker panels?

What is known Biomarkers are laboratory assessments used to detect and characterize diseases and improve clinical decision making. A reliable biomarker for sepsis would assist with earlier diagnosis, improve risk stratification, or improve decision making for care in septic patients [135–137]. Risk stratification and prognostication in sepsis is of particular importance because high-risk patients may benefit from earlier clinical interventions, whereas low-risk patients may benefit from not undergoing unnecessary procedures. Prognostication in sepsis is currently done mostly via clinical criteria (e.g., organ dysfunction and/or presence of shock) and blood lactate levels. While numerous biomarkers have been evaluated in sepsis, none has sufficient accuracy to be utilized in clinical practice. The most commonly used biomarker in septic patients is procalcitonin, but its utility (though still debated) is predominantly to discontinue antibiotics in septic patients when levels fall. Preliminary studies suggest stratification using omics techniques are able to identify high risk patients.

Gaps in knowledge/critique of evidence It is unclear if the absence of acceptable predictive validity in a single biomarkers means (a) we have not yet found the correct biomarker, (b) we have inadequately studied the correct biomarker, or (c) there is no single biomarker that is predictive in sepsis, owning to its heterogeneity. Omics approaches that can generate a "molecular fingerprint" for risk validation and possibly treatment are promising; however, published studies have not been validated. Further the best approach (genomics, transcriptomics, proteomics, metabolomics, epigenetic approaches, etc.) are unclear both from accuracy and feasibility in terms of timeliness and cost.

Future directions Research should continue into whether a single or multiple biomarker have acceptable predictive value to predict development or progression of sepsis, prognosis from sepsis (including need for ICU admission) and/or response to therapy. Existing preliminary studies with omics, endotypes and epigenetic analysis should be validated by research groups outside of those who developed them. Additional research should also be performed to refine and expand existing models and/or to create new biomarker/molecular fingerprints in sepsis.

Post-ICU

What is the attributable long-term morbidity and mortality from sepsis?

What is known As recognition of sepsis increases globally and compliance with best practice improves, the short-term mortality from sepsis appears to be improving,

although the degree to which this is occurring is controversial [131]. While this is obviously encouraging, this leads to an increase in the number of sepsis survivors globally, which represents an additional burden to the heath-care systems in terms of rehabilitation, long-term care and support to caregivers. It is important here to distinguish between acute mortality directly related to the initial insult and late (or post-acute) mortality in patients who survive after hospital discharge. The current knowledge about late sepsis-attributable mortality is limited. Select older data coming from high income countries suggest that sepsis survivors have worse long-term outcomes [138, 139]. A recent systematic review of 43 studies, among which only 16 had control arms to allow assessment of attributable mortality, failed to clearly demonstrate a causal relationship between sepsis and post-acute mortality [140]. This systematic review raised the alternative hypothesis that the increased mortality after sepsis was probably related to the pre-existing disease comorbidity. The review's conclusion was subsequently challenged by two well-designed studies. One study showed that mortality was increased, compared with matched non-hospitalized controls, non-septic infected hospitalized patients and patients admitted with sterile inflammatory conditions [141]. Another study demonstrated that septic patients had higher mortality than matched controls from the general population and subjects who were hospitalized for a non-septic cause [142]. Data from newer cohorts with appropriate controls have also shown that sepsis survivors have a higher risk of hospital readmission which is associated with an increased risk of death [143–145]. Since some of these readmissions are caused by ambulatory care sensitive conditions [143], it is possible that some percentage of these readmissions is preventable.

It is useful to organize the broad domain of morbidity in terms of the Post-Intensive Care Syndrome framework [146], which divides post-critical illness morbidity into (a) cognitive impairment; (b) emotional impairments; and (c) physical disability; as well as (d) increases in specific disease states. There are data to suggest sepsis causes an acute and enduring worsening of cognitive function among survivors [147, 148]. There are conflicting data on emotional impairment with some studies suggesting increased rates of psychiatric diagnoses [149] and others suggesting little change in rates of self-reported depressive symptoms [150] albeit with elevated pre-sepsis symptom burden. Multiple cohorts describe a clear high burden of psychological problems among survivors, including anxiety and post-traumatic stress disorder, regardless of whether it is pre-existing, unmasked, or truly caused by the sepsis or other critical illness [151–154]. These data are indirect, however, as they come from non-septic critically ill patients or exclusively elderly septic patients. Disability rates also appear to be increased for years in survivors of sepsis compared to their pre-ICU levels, at least among older Americans and are high in many populations, driving poor measured health-related quality of life [148, 155–158]. While there have been no systematic efforts to map the specific conditions for which septic patients are at increased risk, there are suggestions of increased rates of malignancy, readmissions for a new sepsis episode, high rates of new cardiovascular diseases and residual immune dysregulations [142, 143, 159–163]. Many septic patients develop new comorbidities such as chronic kidney failure, the mechanisms of which may be different than in patients with non-septic acute kidney injury [164]. Other potential sepsis-associated long term consequences include frailty and an altered microbiome [165, 166]. Unfortunately, many studies in this domain are vulnerable to biases from insufficient characterization of pre-sepsis levels and trajectories of illness [167].

Gaps in knowledge/critique of evidence The specific burden of sepsis morbidity is inadequately characterized, particularly in terms of treatable conditions and competing risks. In addition, while significant contributions have been made regarding the four elements of post intensive care syndrome, the literature is still conflicting at times, incomplete at times, and at risk for bias. The impact of sepsis on caregivers is also inadequately described, including ways in which caregivers provide effective support, and the ways in which supporting caregivers may improve the support of patients. Finally, low and middle-income countries harbor 85% of all sepsis cases. Although mortality rates are higher, thus generating less survivors, the burden to the heath-care system has not been characterized, which may lead to an even higher burden given that these systems are less prepared in terms of rehabilitation capacity, chronic care facilities and support to caregivers.

Future directions More studies are needed to assess the attributable mortality of sepsis (both short-term and late) assessing pre-illness trajectory, confounding factors, and appropriate control groups. Studies using advanced matching techniques to distinguish par subgroups of sepsis from those of other ill and/or critically ill patients at risk of acquiring sepsis are needed. More comprehensive studies are required to determine to what extent sepsis causes all elements of the post intensive care syndrome and whether this differs between sepsis and other causes of ICU admission. Next, understanding the causes of readmission could potentially lead to the determination of preventable causes. Finally, since pre-, intra- and post-hospital resources may play a crucial role in potentially preventable causes of long-term morbidity and mortality,

studies need to be performed in diverse settings, and not just high income countries.

What are the predictors of sepsis long-term morbidity and mortality?

What is known Evidence regarding the extent to which sepsis causes late morbidity and mortality is generally low level and has limited the measurement of a causal relationship between different groups. In 16 studies reported in a systematic review with non-sepsis controls, the main predictor variables for post-acute mortality were age, male sex, tobacco use, health-care associated pneumonia, use of immunosuppressant drugs, HIV infection, cancer, previous cardiovascular or cerebrovascular disease and the degree of organ dysfunction [140]. However, even in well-controlled studies, it is difficult to identify among these factors those related to the sepsis-attributable mortality. A recent controlled study showed that late excess mortality was higher in patients with 3 or more organ dysfunctions, even after adjusting for acute mortality differences [141]. Another recent study observed these [141] effects were significantly higher in male patients, younger patients, those with higher Charlson Comorbidity Index scores, those with higher numbers of organ failure, those admitted to intensive care units, those with shock, and those who required mechanical ventilatory support [142].

Gaps in knowledge/critique of evidence The causal relationship between sepsis and specific subsequent morbidity has been inadequately characterized. Composite outcomes such as quality of life may dilute the ability to measure specific prognostically or mechanistically relevant associations due to poor reliability [168]. It is unclear to what extent acute burden of illness under current supportive technology is correlated with longer-term burden of illness. For instance, some conditions (e.g. acute hypoxic respiratory failure) may be difficult to manage in the inpatient setting, but not strongly associated with worse long-term outcomes among those who survive the acute setting [169]. In addition, many studies do not distinguish between predictors that are prognostically relevant among survivors and those predictors that are mechanistically relevant, which can lead to selection bias.

Future directions More studies are needed to assess the sepsis attributable mortality assessing pre-illness trajectory, confounding factors, and appropriate control groups both in well-resourced setting and resource-limited settings. Approaches to rapidly retrospectively characterize patients' pre-sepsis illness and morbidity trajectory are needed, particularly methods that can use indirect measures such as patterns of past hospitalizations, nursing home use, activity as recorded in personal devices (e.g. smartphones, fitness trackers or proxy reports [170–172]. Studies using advanced matching techniques to distinguish subgroups of sepsis from those of other ill and/or critically ill patients at risk of acquiring sepsis are also needed. Finally identification of potential modifiable risk factors is important to design interventional trials.

Are there potential in-hospital interventions that can impact long term outcomes?

What is known An implication of the data reviewed in questions 1 and 2 in this section is that sepsis-attributable late morbidity and mortality might be amenable to in-hospital interventions. There is strong clinical and physiologic plausibility that interventions considered as best practice with respect to short-term outcomes will also translate into improved long-term mortality and morbidity. Credible in-hospital interventions for which long-term consequences should be considered include (but are not limited to) (a) sepsis screening and detection strategies, (b) ICU triage and use of ICU, about which there is conflicting evidence in terms of short-term mortality in the United States and France, at least among elderly patients [173, 174], (c) alternative antibiotic regimens, including empiric strategies, culture guidance, and de-escalation strategies, and the ABCDEF bundle [175]. Ultimately, however, our knowledge about the relationship between in-hospital interventions and long-terms outcomes is limited, which precludes any definitive statements about the impact of such interventions.

Gaps in knowledge/critique of evidence There is no systematic review assessing this issue and concrete evidence linking in-hospital intervention and long-term outcomes is generally lacking. In addition, there are no data from low and middle-income countries. Since previous studies suggest that compliance with best practice standards might be lower in these settings, potential associations between in-hospital interventions and long-term outcomes need to be specifically addressed in low and middle-income countries.

Future directions Epidemiological studies assessing the association of in-hospital interventions are needed with adequate controls and controlling of confounding factors and selection bias. In addition, long-term follow-up of patients undergoing randomized trials in-hospital may help to clarify whether intervening in the hospital impacts long-term outcome. Currently, most studies do not examine long-term outcomes because of either cost or feasibility issues, yet the opportunity to determine the lasting (or transient) impact of in-hospital interventions is crucial in understanding long-term patient well-being.

Are there potential post-discharge interventions that can improve outcomes?

What is known The optimal strategy for rehabilitation programs and post discharge outpatient clinics aiming to improve quality of life and long-term sepsis mortality is unknown. Two trials that addressed this issue in critically ill patients (not specifically with sepsis) failed to show improved outcomes [176, 177]. Hospital readmissions for ambulatory care sensitive conditions are more common after sepsis than after matched controls, suggesting that effective outpatient care might have an impact in reducing re-hospitalization and, consequently, might influence long-term morbidity and mortality [143]. Despite a relative paucity of evidence to support their use, there is growing use of practices targeting the critically ill, which will, by definition, capture many septic patients. In the United Kingdom, the NICE guidelines recommend a post-ICU follow-up review after 2–3 months for all adult patients who stayed in critical care for more than 4 days and were at risk of morbidity [178]. They also state that health care systems should ensure that any adult who has had a critical care stay can be reassessed if they self-refer at any time. A model integrating early, time-limited post-ICU follow-up (including nurses, physicians, physical therapists, pharmacists, social workers, and peer support) is also being disseminated across Scotland [179]. In the United States, there is growing interest in both post-ICU clinics and post-ICU peer support models [180]. A growing number of United States hospitals report focusing on sepsis as part of the Centers of Medicare and Medicaid Services (CMS) program Partnership for Patients that aims to a 12% reduction in 30-day readmissions [181].

Gaps in knowledge/critique of evidence There is no systematic review assessing this issue, nor have most of the currently adopted models been subject to rigorous comparative effectiveness research. In addition, to our knowledge there are no data from low and middle-income countries.

Future directions Studies aiming to assess the impact of rehabilitation and the long- term follow up of septic patient patients in rehabilitation clinics are needed.

Basic/translational science

What mechanisms underlie sepsis-induced cellular and sub-cellular dysfunction?

What is known Specific functional abnormalities have been reported in essentially all tissues/organs following sepsis. Some evidence suggests that sepsis causes a global defect in a basic sub-cellular function that could lead to the development of dysfunction in many different cell types irrespective of their specific function or location. For example, a defect in mitochondrial oxidative phosphorylation has been demonstrated in multiple cell types [182–184]. The resulting energy deficit could disable cell-specific functions. Conversely, each cell or type of cell may develop a specific defect or manifest dysfunction in a unique manner. For example, secretory function in monocytes and lymphocytes increases, elevating cytokine production [185], while elaboration/release of surfactant or surfactant proteins by type 2 pulmonary epithelial cells [186–188] or of hormones by endocrine or pituitary cells decrease [189–192]. Similarly, apoptosis increases in lymphocytes, dendritic cells and the gut epithelium, while apoptosis is delayed following sepsis in neutrophils (and is unaffected in multiple other cell types) [193–196]. Finally, dysfunction in a single type of cell that is present in virtually all organs could underlie cell- and organ-specific dysfunction. For example, endothelial cells, which are present in all tissues, actively produce inflammatory mediators and coagulation intermediaries during sepsis, and contribute to sepsis-induced vascular dysfunction and leak [197, 198].

Gaps in knowledge//future directions Does a global defect that is shared by multiple cell types underlie all forms of sepsis-induced cellular dysfunction? Are there unique mechanisms of dysfunction that are specific to different types of cells? Do cells of similar embryologic origin (e.g., epithelium) become dysfunctional in ways that differ from other types of cells? Do cells with similar functions (e.g., elaboration/release of proteins, lipids etc.) develop unique forms of dysfunction that differ from that of cells with different basic functions (e.g., all cells that contract)? Since endothelial cells are present in virtually all organ systems and may directly modulate organ function, does endothelial cell dysfunction underlie dysfunction in other organ system? Conversely, because crosstalk occurs between virtually all organ systems and may directly modulate organ function, is there are an overarching method in which cells communicate to cause dysfunction on other organ systems? Finally, what are the mechanisms triggering these cellular alterations and what could be the interplay with tissue hypoperfusion?

How does sepsis alter bio-energetics and/or metabolism (both enhancement and failure)?

What is known Sepsis dramatically alters bio-energetics and/or metabolism [199, 200]. Sepsis increases metabolic rate, as reflected in oxygen consumption and overall substrate utilization [201]. However, this is paradoxically associated with a reduction in ATP utilization in many tissues, which occurs in concert with maintenance of ATP abundance, suggesting that the decreased use reflects an attempt to conserve ATP availability [202, 203]. Decreased activity in electron transport chain complexes I, III, IV and ATP synthase has also been demonstrated

[183, 184]. Sepsis is also known to alter substrate preference, with a decrease in the utilization of glucose (glucose intolerance) relative to fat and protein [204, 205]. As a result, septic patients tend to be hyperglycemic. In later stages oxidation of fatty acids may also be impaired, as reflected in elevated serum levels of lipoproteins, free fatty acids and triglycerides. Glycolysis is favored over oxidative phosphorylation despite adequate oxygen availability ("aerobic glycolysis", sometimes called the Warburg Effect) [206–208]. There is accelerated catabolism of skeletal muscle and perhaps smooth muscle as well [209]. In addition, micronutrient (e.g., vitamins, trace metals) effects are also impaired, reflecting either deficiency or altered activity [210, 211]. In addition, abnormalities are noted in the level and/or effectiveness of most hormones in sepsis [192].

Gaps in knowledge/future directions Are changes in energetics observed in all cells or are they cell-type specific? Are defects affecting energetics present only in mitochondria or are there changes in other sub-cellular structures? What mechanisms mediate alterations in oxidative phosphorylation? What underlies the altered activity in specific electron transport chain complexes? What mechanisms alter sepsis-induced changes in pathway (e.g., glycolysis, beta-oxidation, nitrogen cycle), substrate (e.g., carbohydrate, fat, protein, micronutrient), and/or cell-specific (e.g., cardiomyocyte, hepatocyte etc.) metabolism? What mechanisms underlie sepsis-induced defects in endocrine activity? How does sepsis affect brain circuits that control metabolism? Since cytokines alter metabolism in incompletely understood ways, how do cytokines alter metabolic pathways (and which ones are responsible)? Do metabolic pathways influence inflammation, and if so, how?

How does sepsis (and/or approaches used to manage sepsis) alter phenotypes and interactions in the host microbiome and do alterations in the microbiome effect outcomes?

What is known The microbiome contains 40 trillion organisms, the same number of cells as in the host patient [212]. While the majority of bacterial species and diversity of the microbiome reside within the gut lumen, the microbiome includes all microorganisms residing within (mouth, lungs, gut) or on (skin) the host. Microbial diversity is enormous with 1000 different species of bacteria and over 2 million bacterial genes [212, 213]. Sepsis leads to a rapid (within 6 h) decrease in microbial diversity [214]. Whereas the most common microbe makes up 25% of the microbiome in healthy patients, a massive diversity crash causes results in the most common microbe making up 95% of the microbiome in ICU patients [215]. These changes appear to result from both the underlying disorder (sepsis) and its treatment (antibiotics), which by definition alter the microbiome [216–222]. Further, microbes alter their virulence in response to both the internal host environment (availability of phosphate) and treatments in critically ill patients (opiates) [223–225]. Bacteria in pre-clinical models of sepsis can be tricked into "believing" that the host environment is non-toxic, preventing the development of virulence factors that would ordinarily occur in sepsis, leading to survival advantage in septic rodents [226]. Microbes also possess the capacity for quorum sensing in which individual cells can work together to collectively respond to the environment [227, 228].

Gaps in knowledge/future directions What mechanisms underlie the specific, sepsis-induced changes in the microbiome? Are these reversible? If so, how? How do alterations in the microbiome affect the host response? Which components of the microbiome are responsible? Is it possible to restore a healthy microbiome in the setting of clinical therapies that continue to alter the microbiome? Does the site of bacteria within the microbiome make a difference and can specific host locations be targeted (for instance, the respiratory microbiome)? Does restoring a healthy microbiome improve outcomes in patients (note: this is more of a clinical question than a basic science question since fecal microbial transplant, probiotics, prebiotics, synbiotics and selective decontamination of the digestive disease system are currently in clinical use in select environments)?

What mechanisms initiate, sustain and terminate recovery?

What is known Aside from therapy targeting the specific infection in the ICU, treatment for sepsis is nonspecific and supportive. In spite of this, it is implicitly understood by clinicians that cells and organ systems must recover over time in sepsis survivors despite the absence of therapy aimed at cellular/organ recovery. The study of mechanisms behind recovery in sepsis has only recently become an area of focus in basic/translational sepsis research, and thus relatively little is understood. Intrinsic to recovery is the return of function at subcellular, cellular, and multicellular/organ levels, and within the immune, metabolic, endocrine, intestinal, vascular, neurologic, etc. systems. Recovery may be affected by specific mediators and systems that participate in the initiation and development of sepsis-associated responses. Examples include lipids (resolvins, lipoxins, maresins, prostanoids), autophagy, miRNAs, exosomes, and neuronal activity [190, 229–235].

Gaps in knowledge/future directions What mechanisms and specific mediators are important in recovery? What metabolic, energetic immune, endocrine, intestinal, neuronal and vascular, etc. pathways mediate recovery from dysregulated cellular and subcellular function? Can

sub-cellular, cellular and/or tissue/organ- specific dysfunction be reversed or mitigated by promoting recovery pathways and can the magnitude and time frame of this recovery be accelerated?

Conclusion

This work complements two recent publications on research priorities in sepsis. A 2017 research agenda by 11 international experts in septic shock listed 10 topics to undergo testing over the next 10 years [236]. A 2015 research roadmap by 13 international authors proposed research topics on a wide array of subjects ranging from epidemiology to molecular diagnostics [237]. It is logical that there should be some overlap between the priorities in the different manuscripts, and although each of the potential questions for this manuscript were developed independently of the other two, each previously enumerated priority is proposed in some fashion in the current recommendations. This suggests there is some degree of international consensus regarding sepsis research priorities, and multiple international groups are actively performing research on these priorities. However, the priority list detailed herein additionally includes topics that have been little covered in past efforts, including post-ICU and is broader in scope.

Ultimately, although our understanding of sepsis has greatly increased over the past 20 years, mortality remains unacceptably high. The reasons for this are multifactorial. Significant gaps in knowledge translation from existing evidence to the bedside exist, and efforts aimed to translating best practice to the bedside will almost assuredly result in better outcomes. However, even if all existing best practice standards were followed, significant knowledge gaps remain on a wide array of issues. By taking a maximally inclusive view of priorities in adult sepsis, we hope this overview will serve as a catalyst for research that needs to be performed in sepsis.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-018-5175-z) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

Dr. DeBacker is immediate past president of the European Society of Intensive Care Medicine and has received consulting fees from Edwards Lifesciences, Fresenius Kabi, and Grifols. Dr. Deutschman is a consultant for Enlivix Therapeutix LTD. Dr. Ferrer Roca received honoraria from Toray, MSD, Pfizer and Grifols. Dr. Martin serves on a medical advisory board for Edwards Lifesciences and Grifols. Dr. Antonelli is president of the European Society of Intensive Care Medicine and received honoraria from Pfizer, Toray, Orion, and Air liquid. Dr. Evans is the current co-chair of the Surviving Sepsis Campaign guidelines committee. Dr. Kesecioglu is president-elect of the European Society of Intensive Care Medicine and has received honorarium from Xenios AG. Professor Rhodes is the current co-chair of the Surviving Sepsis Campaign guidelines committee.

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